## REMARKS

Claims 1-8, 14-18, and 26-35, are pending in the present application. Support for the term "antibodies" can be found throughout the specification as filed. In particular, at page 24, lines 3-31. Also, Example 9 provides examples of specific antibodies that show pan-generic cross-reactivity. The term "pan-generic" is supported by the disclosure in Example 9. Furthermore the phrase "less than 1 x $10^6$ CFU per mL" is supported by the disclosure at page 19, lines 12-29. Accordingly, Applicants submit that no new matter has been added by this amendment. Applicants reserve the right to pursue any canceled subject matter in future applications.

Applicants thank Examiners Hines and Elliot for the personal interview of September 9, 2003, during which certain proposed claim amendments and a draft Declaration comparing Applicant's antibodies with commercially available antibodies were discussed. Applicants further thank Examiners Hines and Elliot for the telephonic interview of November 21, 2003. Issues raised in the Office Action are addressed below in the order they were raised by the Examiner.

1. Applicants note that the amendment filed August 13, 2003, has been entered. Claims 1-8, 14-15, 23 and 25-35 are pending.

2. Applicants note with appreciation the withdrawal of the rejections of record under 35 U.S.C. §103.

3. Claims 1-8, 14-18, 23 and 25-35 are rejected under 35 USC §112, first paragraph, as allegedly failing to "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims." [Office Action at page 3]. In particular, the Examiner alleges that "[t]he specification only teaches pan-generic monoclonal antibodies that specifically binds to the gram-positive bacterial antigen lipoteichoic acid clone 96-100 and/or a pan-generic monoclonal antibody that

specifically binds to the gram negative bacterial antigen Lipid A clone 26-5." [Office Action at page 4, lines 3-6].[1] Applicants respectfully traverse this rejection for the reasons set forth below:

First, the application discloses how to make and/or screen for antibodies that are capable of pan-generic cross-reactivity to diverse bacterial species and are capable of detecting clinically relevant amounts of bacterial contaminants in blood or blood products. Example 9, provides examples of specific binding agents having the desired characteristics. In addition, the specification describes how to make antibody derivatives using standard art-recognized techniques at page 24, lines 16-26 and pages 25-26. Furthermore, the application teaches methods for selecting and optimizing antibodies that may be used in the claimed assays at page 26.

It is Applicant' position that once the skilled artisan has the benefit of the teachings of the instant application and realizes that pan-generic antibodies capable of detecting diverse bacterial antigens may be made and/or screened for generating such antibodies is a matter of routine experimentation. We believe that the essence of the claimed invention lies in the discovery that antibodies having such properties may be successfully screened for or generated. The key to obtaining the antibodies as claimed lies in the screening and selection process as set forth throughout the specification as filed. *See*, for example, lines 16-26 of page 24; and lines 6-15 of page 25; and lines 3-22 of page 26.

Secondly, subsequent to filing the application, Applicants have both made and screened for additional antibodies using the experimental methods described in the specification that meet the desired properties. *See* the accompanying Declaration under 37 C.F.R. § 1.132 by Dr. Jeffrey A. Hall. Applicants have provided objective data demonstrating that the Verax antibodies[2] identified using the screening process as described in the application are pan-generic and capable of detecting clinically relevant amounts of bacteria.

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[1] It appears that the Examiner is alleging that the specification is enabling only for a monoclonal antibody clone 96-110 (IgG1) that binds the gram positive bacterial antigen lipoteichoic acid and a monoclonal antibody clone 26-5 (IgG2b) that binds to a gram negative bacterial agent, Lipid A. See Example 9.

Thirdly, as early as 1986, the Court of Appeals for the Federal Circuit has held that making monoclonal antibodies by the hybridoma process taught by Milstein and Kohler as well as screening methods to identify antibodies possessing certain desired characteristics was well known in the art and did not constitute undue experimentation for a person skilled in the art of antibodies. *See, Hybritech Inc., v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (CAFC 1986).

Finally, solely in an effort to expedite prosecution, Applicants have cancelled claims 23 and 25 and amended the remaining claims to recite the term "antibodies" instead of binding agents. Applicants reserve the right to pursue the cancelled subject matter in a future continuation or divisional applications.

In sum, methods for making and/or screening for antibodies having desired properties does not rise to the level of undue experimentation and reconsideration and withdrawal of this rejection is respectfully requested.

4. Claims 1, 3-6, 14, and 16 and 23-24 are rejected under 35 USC §103(a) as allegedly being unpatentable over McLaughlin (of record), Erich et al. (*J. Immunol.* 143(12): 4053-4060 (1989)), Tadler *et al.* (of record), and Fisher et al. (WO 98/57994). In particular, the Examiner states that "it would have been prima facie obvious to modify the analyte detection immunoassay that incorporates a set of binding agents as taught by McLaughlin and Tadler et al., since McLaughlin and Tadler et al., teach antibodies which specifically bind to gram-negative or gram-positive bacteria in order to determine their presence and/or absence wherein the assay is modified to include the pan-generic monoclonal antibodies as taught by Erich et al., and Fischer et al." [Office Action at page 10]. Applicants respectfully traverse this rejection. Applicants show that the combination of references fails to: (A) provide motivation or reasonable expectation of success; and fails to (B) provide the claimed invention. Applicants then discuss certain arguments set forth by the Examiner with regards to the weight to be given to the preamble of method claims and certain secondary considerations that are prevalent in this case.

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[2] Verax antibodies include both antibodies that are disclosed in Example 9 and antibodies that were generated and/or screened for using the methods taught in the specification.

*Lack of Motivation & Reasonable Expectation of Success*

In making the combination, the Examiner admits that McLaughlin fails to teach a pan-generic monoclonal antibody that specifically binds to the gram-negative bacterial antigen Lipid A clone 26-5[3] but argues since Erich et al. disclose a monoclonal antibody that shows extensive cross-reactivity with heat killed as well as live gram negative bacteria the skilled artisan would be motivated to modify the assay to include the antibody as taught by Erich et al. [Office Action at page 7]. Similarly, the Examiner admits that Tadler et al. fails to teach the use of a monoclonal antibody 96-110[4] but argues that since Fischer et al. disclose a monoclonal antibody designated as 96-110 that exhibited strong IgG reactions, the skilled artisan would be motivated to modify the assay to include the antibody as taught by Fischer et al. [Office Action at pages 8-9]. Applicants respectfully submit that this rejection is legally insufficient in that:

(a) there is no suggestion or motivation in the cited art to modify the claimed assay to use either the McLaughlin or the Tadler antibodies to begin with;

(b) there is no suggestion or motivation in the cited art to modify an assay to substitute the McLaughlin antibodies with the Erich antibodies or to substitute the Tadler antibodies with the Fischer antibodies as suggested by the Examiner; and

(c) there is no reasonable expectation leading one to believe that such a combination would result in an effective test for detecting less than $1 \times 10^6$ CFU per mL of bacterial contaminants.

Applicants have previously addressed the deficiencies presented by the McLaughlin and Tadler et al. antibodies in our responses dated October 8, 2002 and April 11, 2003 and in our draft Declaration presented during the Interview dated September 9, 2003. In response to our arguments, the Examiner withdrew all rejections of record based on McLaughlin et al. and/or Tadler et al. and admitted on record that the Tadler et al. antibodies and the McLaughlin

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[3] Presumably, the Examiner means a monoclonal antibody (clone 26-5) that specifically binds to the gram-negative bacterial antigens.

[4] Presumably, the Examiner means a monoclonal antibody (clone 96-110) that specifically binds to the gram-positive bacterial antigens.

antibodies are not pan-generic in nature.[5] Therefore, preliminarily, we see no reason why the skilled artisan would modify the claimed assay to use the Tadler et al. and McLaughlin antibodies to begin with.

Assuming *arguendo*, the skilled artisan were to use the antibodies disclosed by Tadler et al. and McLaughlin in the claimed assay, we believe that there is no suggestion or motivation in the cited art to modify the assay as suggested by the Examiner. McLaughlin teaches an antibody that is capable of detecting Salmonella, Neisseria, and Chlamydia.[6] As stated above, the Examiner agrees that this antibody is not pan-generic in nature. The Examiner then substitutes the Erich antibodies for the McLaughlin antibodies. However, a close review of Erich et al. shows that the Erich et al. antibodies at best react with two (live) bacterial genera: Escherichia and Salmonella. See Table VI. In addition, these antibodies react with the LPS of three heat-killed bacterial genera: Escherichia, Shigella and Salmonella. In effect, the Examiner substitutes an antibody that is cross-reactive with three bacterial genera with another antibody that is also cross-reactive with three *albeit* different bacterial genera. It is Applicant's position that the skilled artisan would not be motivated to make the substitution suggested by the Examiner because Erich et al. fails to provide any reasons for the skilled artisan to do so.

The Examiner admits that Tadler et al fail to disclose a pan-generic antibody. In fact, the Tadler et al. antibody shows binding and detection of four (4) bacterial genera: *Streptococcus*, *Staphylococcus*, *Enterococcus*, and *Clostridium*, but does not indicate the level of detection. See Table 1. However, Tadler et al. only show detection of *S. mutans* and *S. epidermidis* at clinically relevant levels of $1 \times 10^6$ colony forming units (CFU) per milliliter (mL). See Figure

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[5] We incorporate herein the arguments presented against these references in our previous responses.

[6] The Examiner contends that McLaughlin teaches the "immunological detection of an entire class of microorganism." Office Action at page 6. We note that this characterization is erroneous. Because, in actuality, McLaughlin states that based on the discovery of antibodies that bind to three species "*it is possible to* perform a single test for a large number of LPS producing organisms merely by reacting said antibody with a clinical sample" (see column 5, lines 29-34). [emphasis added]. Applicants assert that although McLaughlin states that it would be possible to perform a single test, McLaughlin *did not* actually perform the tests. The courts have held that "obvious to try" is not the standard for an obviousness rejection. *In re O'Farrell*, 853, F.2d 894, 903, 7 USPQ 2d 1673, 1681 (Fed. Cir. 1988).

2. Therefore, in total, Tadler et al. show detection of only two bacterial genera at clinically relevant amounts as required by the claims. The Examiner then substitutes the Tadler et al. antibody with the Fisher et al. antibody to make up for the deficiencies of the Tadler antibodies. However, a review of the Fisher et al. reference shows that Fischer et al disclose binding to ***only*** one bacterial genus: *Staphylococcus*. The Fisher reference discloses that the antibody is capable of treating infections of seven (7) species of Staphylococcus, *S. epidermidis*, *S. hemolyticus*, *S. mutans*, *S. hominus*, *S. aureus*, *S. faecalis*, and *S. pyogenes* (see the Figures). In effect, the Examiner substitutes an antibody that is cross-reactive with least two bacterial species at clinically relevant amounts with another antibody that is taught to be cross-reactive with just one bacterial genus. It is Applicant's position that based solely on the teachings of the Fischer reference a skilled artisan would not be motivated to make the substitution suggested by the Examiner because Fischer et al. fails to provide any reasons to do so.

Applicants respectfully submit that Courts have cautioned against the use of the patentees disclosure as a blueprint to reconstruct the invention from the prior art. See *Interconnect Planning Corp. v. Feil, 227 USPQ 543 (Fed. Cir. 1985).* Applicants specification teaches the unappreciated properties of the Fischer antibody. See Example 9. These properties were further highlighted during the Interview dated September 9, 2003. However, there is no teaching, disclosure, or suggestion of these properties in the Fischer reference. Accordingly, the teachings of the Fischer reference fail to provide any reasons for the combination suggested by the Examiner. It is Applicants' position that although the Fisher et al. reference had been cited in the specification and disclosed to the Examiner from the very beginning, it was used as prior art only after the Examiner became privy to the unexpected properties of the Fisher antibody during the Interview dated September 9, 2003, when Applicants provided a draft Declaration setting forth these properties. Thus, Applicants submit that the Examiner has used improper hindsight in using the disclosure of the Fisher antibodies as described in Example 9 of the instant specification as part of the rejection under 35 U.S.C. § 103. The following Table provides a comparison between the properties of the Fischer antibody taught in the Fischer reference and the properties as taught by the instant application:

| Gram positive bacterial species recognized by the Fisher antibody as taught by the Fischer reference | Gram positive bacterial species recognized by the Fisher antibody as taught by the instant application |
|---|---|
| *Staphylococcus spp.* | *Staphylococcus spp.*<br>*Streptococcus pyogenes*<br>*Group B Streptococcus*<br>*Group G Streptococcus*<br>*Enterococcus faecalis*<br>*Corynebacterium minutissimum*<br>*Clostridium perfringens*<br>*Bacillus spp.* |

As can be seen from the Table, there is no objective evidence or suggestion in the Fisher publication that the antibodies would be reactive outside of Staphylococcus, nor is there any teaching that the antibody would be effective in a blood bank setting for detection of clinically relevant amounts of bacteria. Any pan-generic activity of the Fisher antibody was completely unappreciated in the PCT publication. Moreover, it is well settled law that "[o]bviousness cannot be predicated on what is unknown." *In re Spormann,* 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

*Failure to provide the Claimed Invention*

It is Applicant's position that the proposed combination of references fails to teach or suggest all the limitations of the claims. See In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q 494, 496 (C.C.P.A. 1970). The claims as currently amended require three key elements: (1) screening of donor blood, blood products, and tissue, (2) pan-generic activity of the antibodies, and (3) detection of clinically relevant amounts of bacteria.

Furthermore, a person skilled in the art of blood banking would recognize that there is a distinct difference in diagnostic assays to identify specific bacteria in blood or blood products from patients exhibiting symptoms of infection and screening blood or blood products from healthy and/or asymptomatic donors for bacteria where it is not known *apriori* whether the

donated blood sample: is or is not contaminated; and if contaminated what the bacterial contaminants might be. In the blood banking discipline, the term "donor" is a universally recognized term of art. We provide herewith a Declaration by Dr. Harvey Klein (one of skill in this art) setting forth the meaning of the term "donor" in this art. Dr. Klein states that Federal Law mandates that only healthy and/or asymptomatic subjects are allowed to donate blood. Prior to donating, each individual must undergo a thorough screening process that includes temperature, pulse, blood pressure, hemoglobin content in the blood, and questions about general health, background and travel. See AABB Association Bulletin #99-10, dated December 2, 1999, attached as Appendix B of the Klein Declaration. See also the blood donation eligibility guidelines as set forth by the American Red Cross, attached as Appendix C of the Klein Declaration. If the donor fails any of these questions/requirements, the individual is turned away from the donation center to prevent provision of adulterated components to blood recipients. Thus, in the blood banking arena the term "donor" means a healthy or asymptomatic subject qualified to donate blood.

Often, donors are asymptomatic for infection and donate blood, which is then stored for use. Most contaminants arise from the collection process (e.g., skin introduced into the collection as a result of needle puncture, environmental factors, hair follicles, etc.). Occasionally, subclinical levels of bacteria at the time of donation can expand to levels such that they would cause infection when often transferred to a recipient. The instant claims are directed to method for testing the blood obtained from such asymptomatic donors for bacterial contamination.

Each reference cited by the Examiner, McLaughlin, Erich, Tadler, and Fisher, teach either the identification of specific bacteria, or administration of an antibody in a therapeutic setting to kill a specific bacteria. There are no teachings or suggestions in any of the references that the antibodies could be used in the manner as currently claimed. None of the references teach or suggest even trying to test blood, blood product, or tissue taken from healthy or asymptomatic donors.

*Preamble in Method Claims must be given Patentable Weight*

The Examiner argues that that the preamble of the instant claims has not been given patentable weight. Applicants respectfully disagree with the Examiner's position. The courts have consistently held that for method claims the preamble is given patentable weight when it

breathes life and meaning into the claims. For example, in *Griffin v. Bertina*, 62 USPQ2d 1431 (CAFC 2002), the preamble was directed to a "method of diagnosing" and the specific diagnosis was stated again in the body of the claim; here, the Federal Circuit held that diagnosis was considered to be the essence of the invention that gave "life and meaning" to the manipulative steps. The instant claims parallel *Griffin v. Bertina* in that the preamble recites a method of screening donor blood, blood products, and tissue for clinically relevant amounts of bacteria, the method steps are directed specifically to carrying out the screening, and when found to be free of clinically relevant amounts of bacteria, the claim body recites that the donor blood, blood products, and tissue is useful for transfer to a recipient. Thus, Applicants assert that the preamble of the currently amended claims gives life and meaning to the manipulative steps and should be properly accorded patentable weight.

*Secondary Considerations*

(a) Unexpectedly superior results

Applicants submit herewith a Declaration under 37 C.F.R. § 1.132 by Dr. Jeffrey A. Hall that compares the antibodies that were either taught in Example 9 or that were subsequently made in accordance with the teachings of the specification with commercially available antibodies that are being marketed as being pan-generic in nature. The Declaration shows the superior cross-reactivity to diverse bacterial species and sensitivity of the Verax antibodies.

(b) Skepticism in the art

As discussed in our previous responses, those of skill in this art were skeptical about the effectiveness of immunoassay-based tests because of the lack of common bacterial antigens across the diverse bacterial species. To this end, we provide herewith a Declaration Under 37 C.F.R. § 1.132, from Dr. Stephen Wagner, Director of Cell Therapy at the Holland Laboratory of the American Red Cross, who states that it was believed that no practical immuno-based tests could be developed for detecting bacterial contamination in blood.

(c) Long-felt need and failure of others

In previous replies, Applicants have clearly set forth the failure in the field of blood banking throughout the 1990s to generate an effective test as required by blood banks. Thus, there remains a long-felt need for a rapid and effective test for detecting clinically relevant levels of bacteria immediately prior to transfer to a recipient. Applicants provide herewith a Declaration by Dr. Harvey Klein, Chief of the Department of Transfusion Medicine at the Warren C. Magnuson Clinical Center, National Institutes of Health who has been working in the field of transfusion medicine for over thirty (30) years setting forth the long-felt need in the industry together with the failure of others. Applicants respectfully submit that "the failure of others to satisfy a long-felt need or develop a commercially successful product is evidence of non-obviousness". *Dow Chem. Co. v. American Cyanamid Co., 2 USPQ2d at 1355.*

For the reasons of record and those set forth herein, Applicants respectfully request reconsideration and withdrawal of this rejection.

5. Claims 2 and 15 are asserted as allegedly being unpatentable over McLaughlin, Erich et al., Tadler et al., and Fisher et al. as applied to claims 1 and 14 above, and further in view of Chang et al. (of record) under 35 U.S.C. § 103(a). Applicants respectfully traverse this rejection.

The Examiner's discussion and Applicants' rebuttal of McLaughlin, Erich et al., Tadler et al., and Fisher et al. have been discussed *supra*. The Examiner sets forth at pages 11 of the Office Action that Chang et al. teach that in the absence of a clinically relevant amount of bacteria, blood is transferred to a recipient mammal. Specifically, the Examiner states that "Chang et al. teach it is beneficial to screen blood to prevent contamination".

Applicants respectfully traverse this statement. Applicant reiterate that Chang is directed to the safety of transfer of modified hemoglobin blood substitutes (see column 4 at lines 10-30), *not* to a method of screening blood/blood product for clinically bacteria and found to be free of gram positive and gram negative bacteria for transfusions. Nor is it even directed to the detection of clinically relevant amounts of bacteria at all.

The deficiencies of each of the McLaughlin, Erich et al., Tadler et al., and Fisher et al. publications cannot be cured by the deficiencies of Chang et al. Applicants respectfully request reconsideration and withdrawal of this rejection.

6. Claims 7 and 17 are asserted as allegedly being unpatentable over Tadler et al. (of record) and Fisher et al. (of record) under 35 U.S.C. § 103(a). Applicants respectfully traverse this rejection.

The Examiner's discussion and Applicants' rebuttal of Tadler et al. and Fisher et al. have been discussed *supra*.

It is Applicants' position for the reasons of record and those set forth above that one of ordinary skill in the art at the time the application was filed would not have had a reasonable expectation of success of arriving at the claimed invention by combining the teachings of Fisher et al. and Tadler et al. due to the overwhelming evidence that attempts to create a method for screening blood and blood products for clinically relevant amounts of bacteria throughout the 1990's had consistently failed. Thus, one of ordinary skill in the art at the time the application was filed would not have a reasonable expectation of success that producing the method as currently claimed would be a viable endeavor.

Applicants respectfully request reconsideration and withdrawal of the rejection.

7. Claims 8 and 18 are asserted as being unpatentable over McLaughlin (of record) in view of Erich et al. (of record) under 35 U.S.C. § 103(a). Applicants respectfully traverse this rejection.

The Examiner's discussion and Applicants' rebuttal of McLaughlin and Erich et al. have been discussed *supra*. Applicants respectfully request reconsideration and withdrawal of the rejection.

## CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

Date: December 29, 2003

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